REMARKS

Claims 1-10 and 16-19 are presently pending in the application. Claims 11-15 and 20-22 have been withdrawn from consideration by the Examiner. Please cancel claims 11-15 and 20-22 without prejudice to refiling one or more divisional applications. Claims 1-10 and 16-19 stand rejected. The objection to the drawings has been noted and Applicants are submitting with this response a clean copy of corrected drawings.

Applicants thank the Examiner for the courtesy extended in conducting a helpful interview with undersigned counsel. Although no agreement was reached, the discussion provided helpful insight into outstanding issues. The Examiner has noted in the interview summary that he is concerned as to whether the instant disclosure adequately describes the claimed invention in such full, complete and clear terms that one would reasonably conclude that applicants had in their possession the generic method of claim 1. The discussion focused on the written description and enablement of a prokaryotic cell, a sample, a vector and its requisite origin of replication, a tetracycline repressor and a tetracycline promoter. The Examiner expressed concern over the sufficiency of the description in the disclosure to lead one to conclude that the Applicants had possession of the claimed invention.

Claim 1 has been amended to indicate that the sample analyzed in the assay is a liquid from a liquid or solid sample and wherein the tetracycline repressor is removed from the tetracycline promoter in the presence of tetracycline to activate the promoter. Support for a liquid sample can be found at pages 16 and in Examples 3 and 4 on page 7. Furthermore, as noted at page 7, lines 6-10, the samples can be derived from sources including liquids and solids such as "milk, fish, meat...and the like." Support for the further description of the tetracycline promoter and its functional relationship to tetracycline can be found at page 8, lines 2-12. Claims 3-9 and 16-19 have been amended to point out with particularity the subject matter which applicants regard as the invention. It is believed that these amendments do not constitute new matter, and their entry is requested.

35 U.S.C. § 112 Written Description Rejections

In Paper No. 17, claims 1-10 and 16-19 were rejected for lack of a written description. The Examiner has noted that the Applicants are seeking protection for a generic claim using cells and constructs that have been defined functionally. The Examiner further notes a purported insufficiency of the number of working examples provided in the present application. The Examiner has asserted that University of California v. Eli Lilly, 119 F.3d at 1568, 43 U.S.P.Q.2d 1398, 1406, provides appropriate guidance for what is required to meet the written description requirement. The Examiner is of the opinion that Lilly, in citing In re Angstedt, 537 F.2d 498, 190 U.S.P.Q.2d 214 (CCPA 1976), provides the guidance for what level of support is necessary to satisfy the generic claim. The essence of the Examiner's rejection of the claims is that the specification does not disclose the testing of any species of bacteria, with any sample, with any tet promoter/repressor and with any light emitting enzyme. The Examiner is further of the opinion that the specification discloses but "a single construct and but a single type of cell." The Examiner notes that in Angstedt, the disclosure of forty working examples sufficiently described subject matter of claims directed to a generic process.

Applicants disagree with the Examiner's analysis of the extent of disclosure submitted in the present application. As discussed *infra*, the specification clearly contemplates and discloses the use of the tet system fused to a light emitting enzyme to detect the presence of tetracycline in a sample. The specification discloses that the invention can be practiced in numerous bacterial strains and with numerous samples by exposing the sample in liquid form to bacteria containing the light emitting enzyme under the control of the tet repressor/promoter system. Furthermore, it is respectfully submitted that Angstedt is not applicable to a written description analysis. Angstedt, as noted by the Federal circuit in Lilly, "...**is an enablement case**." 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406 (emphasis added; See also In re Angstedt, 537 F.2d 498 at 501; "the primary issue is 'whether the claims on appeal read on subject matter as to which the specification is not enabling'"; citing the PTO Board of Appeals).

In asserting a lack of an adequate written description for the present claims, the Examiner has disregarded the Patent and Trademark Office Guidelines for performing a written description

analysis. Under present U.S. patent law, functional descriptions of inventions are adequate for written description compliance, provided that they would convey to a skilled artisan what was invented and that one skilled in the relevant art would know how to carry out the invention. As stated in the Decision Tree at page 3 of the "Synopsis of Application of Written Description Guidelines," the first step in determining whether adequate written description for a genus exists is to determine whether the art indicates substantial variation among the species within the genus of the claimed subject matter. Next, one must determine whether there is a representative number of species implicitly or explicitly disclosed. Next, it must be determined whether the applicant was in possession of the "necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed."

As noted *supra*, elements of concern to the Examiner are a prokaryotic cell, a sample, a vector and its requisite origin of replication, the tetracycline repressor and the tetracycline promoter. The claims have been amended to recite a method wherein a liquid is mixed with bacteria having a light emitting enzyme under the control of the tet repressor/promoter system wherein tetracycline can be detected in the liquid by detecting luminescence in the cells. These are the common attributes or features of the elements possessed by the members of the genus. As noted at page 9, lines 6-17, many other bacterial species are described as suitable for practicing the invention using these necessary and common elements. Furthermore, it is noted at page 9, lines 25-28, that the reporter system can be integrated into any other microbial strain "...containing the necessary secondary regulatory sequences such as correct ribosomal binding region, transcriptional termination, etc."

In University of California v. Eli Lilly, 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406 and Fiers v. Revel, 984 F.2d 1164, 1169, 25 U.S.P.Q.2d 1601, 1605 (Fed. Cir. 1993) the Federal Circuit addressed situations in which the applicant sought claims that encompassed novel DNA molecules that, as of the filing date, could not be described in terms of structure, formula, chemical name or physical properties. Instead, the claims and the supporting description defined the DNA molecules by reference to their function (coding for the proteins of interest) and general methods for their synthesis. The Court held that such descriptions of DNA molecules were inadequate for compliance

with the written description requirement of §112, ¶ 1. Eli Lilly, 119 F.3d at 1568, 43 U.S.P.Q.2d at 1406; Fiers v. Revel, 984 F.2d at 1169, 25 U.S.P.Q.2d at 1605.

The Examiner's reliance on Lilly and Angstedt in this case is misplaced. The facts of Lilly are quite different from those of this case. In Lilly, the applicants attempted to claim a DNA for human version of a gene where they had only described the rat version. While the nucleotide sequence of a DNA molecule often is essential to show that the patent applicant possessed the invention, the same is not true of other claims to biological materials. The deficiencies and inapplicability of Angstedt have been noted supra. Furthermore, functional descriptions of inventions are adequate for § 112, paragraph one, written description compliance, provided that they would convey to a skilled artisan what was invented. In re Hayes Microcomputer Prods. Patent Litigation, 982 F.2d 1527, 1534, 25 U.S.P.Q.2d 1241 (Fed. Cir. 1992) held that disclosing a microprocessor capable of performing certain functions is sufficient to satisfy the requirement of § 112, first paragraph, when one skilled in the relevant art would understand what is intended and know how to carry it out.

In the present application, the Applicants have clearly conveyed to a skilled artisan what was intended and what was invented. Applicants described a prokaryotic cell having a vector with a light emitting enzyme under the control of a tetracycline inducible promoter system, wherein the light emitting enzyme is transcriptionally activated in the presence of tetracycline and expression of the enzyme is detected in the cell. Applicants described an assay for the presence of tetracycline by introducing a functional system into a bacterial species. Applicants further described that said system could be introduced into other **known** species, provided that the necessary **known** regulatory elements sufficient for expression of the system were provided. Such regulatory elements were well known at the time of Applicants' invention for numerous other species other than *E. coli*, including bacteria, yeast and eukaryotic cells. Numerous cells other than *E. coli* were also disclosed as being useful for expressing the Tet system encompassed in the methods of the invention.

The Patent and Trademark Office permits a description in terms of "functional characteristics when coupled with a known or disclosed correlation between function and structure." Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, ¶ 1 Written Description Requirement,

66 Fed. Reg. 1099 (June 5, 2001). In the case of the present invention as embodied in the claims, one of minimally competent skill in the art would know that the functionally described system could be expressed in other bacteria and other gram negative and gram positive bacteria suitable for expression of the system were **described**. The written description as filed is presumed to be adequate and the Examiner has the burden of providing "sufficient evidence or reasoning as to the contrary...to rebut the presumption [,]...presenting by a preponderance of evidence why a person skilled in the art would not recognize in the applicant's disclosure a written description of the invention defined by the claims" MPEP2163.04 citing In re Wertheim, 541 F.2d 257, 262-3, 191 U.S.P.Q.2d 90, 96-97 (C.C.P.A.1976). The Examiner has not met this burden, instead citing inappropriate case law and simply asserting that the number of working examples was insufficient to satisfy the written description requirement.

In view of the amendments to the claims and above arguments, it is believed the claims are in condition for allowance and Applicants request that the rejection of the claims under 35 U.S.C. § 112, first paragraph for lack of written description be withdrawn.

35 U.S.C. § 112 Enablement Rejections

The Examiner has rejected claims 1-10 and 16-19 under 35 U.S.C. §112, first paragraph for lack of enablement with respect to the scope of the claims. It is submitted that the Examiner is in error with respect to this rejection, especially with his analysis of the Wands factors.

The present claims are directed to a method for determining tetracycline in a sample utilizing recombinant prokaryotic cells comprising a vector containing a DNA fragment encoding a light producing enzyme under transcriptional control of a tetracycline repressor and a tetracycline promoter. Any light producing enzyme can be used, so long as it is under control of the tetracycline repressor and the tetracycline promoter. The system can be placed in any vector which may be used in prokaryotic cells -- any prokaryotic cell which is compatible with the vector. Applicants have disclosed that the system can be placed in other bacteria as long as the proper regulatory elements are incorporated. Any sample can be utilized, so long as it is eventually mixed with the cells in liquid form.

As with the written description requirement of section 112, the "examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." MPEP2164.04, citing In re Wright, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed.Cir.1993). Furthermore, it is incumbent upon the Patent Office to

> "explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

M.P.E.P. § 2164.04, citing In re Marzocchi, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

The Examiner has asserted that the claims are not enabled, stating that several man-years of experimentation with little reasonable expectation of success would be needed, without providing any reasons or evidence to support his contention. Such contentions, without scientific reasons or evidence are not sufficient to sustain an enablement rejection. In re Marzocchi, 169 U.S.P.Q. 367 (CCPA 1971). As provided in the M.P.E.P., if doubt arises about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation, the examiner "should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation." M.P.E.P., 2164.04. Furthermore, while references may not be required for the Examiner to meet his or her burden, "specific technical reasons are **always** required. Id emphasis added. To determine enablement, the specification is considered in light of the knowledge in the art at the time of the invention. When considering the adequacy of enablement for a generic claim, the M.P.E.P. states that proof of enablement is required for other members of the genus "...only where **adequate reasons** are advanced by the Examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." M.P.E.P. at 2164.02.

As noted previously by Applicants, recombinant DNA techniques are well established in the art. In view of the vast knowledge in the art, the preparation of vectors which are suitable for transforming prokaryotic hosts does not require undue experimentation. That is, skilled artisans know which vectors can be used with any given host. Transformation techniques for most prokaryotic hosts are also well known in the art. Thus, the transformation of hosts with such vectors also does not require undue experimentation. DNA encoding light producing enzymes and DNA containing tetracycline repressor and tetracycline promoter are well known in the art. The use of *tet* system in other vectors and other hosts was demonstrated with numerous references provided with Rule 132 Declaration of Dr. Matti Karp submitted previously. These references clearly demonstrate that at the time of Applicants' invention, the *tet* system was well known to work in other vectors and other hosts, including even mouse and other eukaryotic cells. Thus, the preparation of vectors containing the elements disclosed in the specification, the preparation of host cells containing such vectors and the expression of the construct in such host cells require no undue experimentation. Numerous examples of techniques for obtaining liquid samples for analysis were noted previously in Applicants response and Dr. Karp's Rule 132 Declaration.

The specification clearly describes the components of the vector present in the prokaryotic cells which are used to practice the claimed method. The novel aspect is the use of a prokaryotic cell containing a vector for the determination of tetracycline in a sample. The vector comprises a nucleotide sequence encoding a light producing enzyme under the transcriptional control of a tetracycline repressor and a tetracycline promoter. Each of these elements is known to a skilled artisan. The novel aspect of the gene for a light producing enzyme being under the transcriptional control of a tetracycline repressor and tetracycline promoter is fully disclosed in the specification, as is the activation and detection of the light producing enzyme in the presence of tetracycline. Thus, Applicants have supplied the novel aspects of the invention, and the specification does not rely on the knowledge of a skilled artisan to supply any novel aspects.

The relative skill in the art is lower than that suggested by the Examiner. The skill in the art at the time that recombinant DNA inventions were first made, e.g. in the 1970's, was certainly at the level of individuals with a Ph.D. in biochemistry. However, such a level of skill for the ordinary

artisan is no longer that high. Many non-Ph.D.'s perform these techniques on a daily basis in high school, college, university and industrial settings. Skilled technicians can readily isolate and clone sequences when provided with sufficient information as to what is to be isolated and cloned. Texts are available in the art which provide all of the necessary instructions for making recombinant DNA, recombinant cells and growing such recombinant cells in **numerous** bacterial strains. These references were well known to persons of skill in the art at the time of the invention. Thus, a person of skill in the art would at least know the basics of microbiology and molecular biology, which would enable the practice the claimed invention on the basis of the present disclosure.

Dr. Matti Karp previously submitted a Rule 132 Declaration demonstrating the state of the art at the time of the present invention, both with respect to the use of other vectors and host cells. The Rule 132 Declaration discussed numerous references that rebut unsupported conclusions reached by the Examiner in his rejection. With respect to the Examiner's observation that this Declaration contains the remarks of "...one who holds an interest in the proceedings now before the Office[,]" this observation is of no consequence to the requirements for enablement or written description. As provided in the M.P.E.P., "[a] declaration or affidavit is, itself, evidence that must be considered. M.P.E.P. at 2164.05. Furthermore, the "weight to be given a declaration or affidavit will depend on the amount of factual evidence the declaration or affidavit contains to support the conclusion of enablement." Id. As noted above, the Examiner bears the burden of demonstrating that the claims are not enabled, and the Examiner has not met ths burden.

In view of the amendments to the claims and above arguments, it is believed the claims are in condition for allowance and Applicants request that the rejection of the claims under 35 U.S.C. § 112, first paragraph for lack of enablement be withdrawn.

35 U.S.C. § 112, Second Paragraph Rejections

Claims 1-10 and 16-19 were rejected as indefinite. The claims have been amended where appropriate to overcome these rejections.

With regard to the Examiner's assertion that claims 8 and 9 are indefinite for failing to recite any steps involved in the method/process, it is respectfully submitted that the steps involved in the

method process are described in claim1, from which these claims depend. Nevertheless, the claims have also been amended to recite an assay as in claim 1 wherein said prokaryotic cells are an antibiotic sensitive mutant strain (claim 8) or an assay utilizing an instrument from a Markush group (claim 9) defining a set of instruments that can be used in said detection of luminescence step from claim 1.

In view of the amendments to the claims and above arguments, it is believed the claims are in condition for allowance and Applicants request that the rejection of the claims under 35 U.S.C. § 112, second paragraph for being indefinite be withdrawn.

35 U.S.C. § 101 Rejections

Claims 8 and 9 were rejected for claiming the recitation of a use without setting forth any steps involved in the process. Applicants respectfully submit that the steps involved in the process of these claims are recited in claim 1, from which these claims depend. These claims as amended recite cells or instruments utilized in the method of claim 1.

In view of the amendments to the claims and above arguments, it is believed the claims are in condition for allowance and Applicants request that the rejection of the claims under 35 U.S.C. § 101, for lack of utility be withdrawn.

In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes and reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

RESPECTFULLY SUBMITTED,					
NAME AND REG. NUMBER	Michael J. Moran, Registration No. 42,013				
SIGNATURE	Michael J Moran		DATE	9/19/02	
Address	Rothwell, Figg, Ernst & .+Manbeck 1425 K Street, N.W.				
City	Washington	*State*	D.C.	*Zip Code*	20005
Country	U.S.A.	*Telephone*	202-783-6040	*Fax*	202-783-6031

Attachments: Marked-Up Copies of Amendments

Marked-up Copy of Amended Claim

1. (Three times amended). A method for the determination of the presence of tetracycline in a liquid from a liquid or solid sample, characterized in that

- the [sample] liquid is brought into contact with recombinant prokaryotic cells encompassing a DNA vector including a nucleotide sequence encoding a light producing enzyme under transcriptional control of a tetracycline repressor and a tetracycline promoter, wherein said tetracycline repressor is removed from the tetracycline promoter in the presence of tetracycline, which causes said promoter to activate expression of said enzyme

- detecting the luminescence emitted from the intact cells, and

- comparing the [emitted] luminescence emitted from said intact cells to the luminescence emitted from control cells brought into contact with a liquid lacking [in a control containing no] tetracycline

- wherein a detectable luminescence higher than a luminescence of the control cells indicates the presence of tetracycline in the sample.

3. (twice amended). The method according to claim 1 characterized in that the DNA vector is a plasmid containing [the] luxCDABE genes (SEQ ID NO:3), tetracycline repressor (TetR) (SEQ ID NO:11) and tetracycline promotor (TetA) (SEQ ID NO:9) from *Tn*10.

4. (amended). The method according to claim 3 characterized in that the DNA vector is [the] plasmid pTetLux1 (SEQ ID NO:3).

5. (twice amended). The method of claim 1 characterized in that

the DNA vector is a plasmid containing [the] an insect luciferase gene (SEQ ID NO:1), tetracycline repressor (TetR) (SEQ ID NO:11) and tetracycline promotor (TetA) (SEQ ID NO:9) from *Tn*10, and that

D-luciferin is added to the mixture of the sample and the cells in order to initiate the luminescence of the cells.

6. (amended). The method according to claim 5 characterized in that the DNA vector is [the] plasmid pTetLuc1 (SEQ ID NO:1).

7. (twice amended). The method according to claim 1 characterized in that [the sensitivity of the analysis with respect to the] the presence of said tetracycline is [controlled] determined by

increasing or decreasing the concentration of divalent metal ions, e.g. magnesium ions, or adjusting the pH, or

combined adjusting of the divalent metal ion concentration and the pH.

8. (three times amended). The method of claim 1 characterized in that the [sensitivity of the analysis with respect to the tetracycline derivative is increased by the use of] cells [which] are antibiotic sensitive mutant strains.

9 (three times amended). The method of claim 1 characterized in that [the] said luminescence is [measured] detected using an instrument selected from the group consisting of X-ray or photographic film, a CCD-camera, a liquid scintillation counter or a luminometer.

16. (amended). The method according to claim 2 characterized in that the DNA vector is a plasmid containing [the] luxCDABE genes (SEQ ID NO:3), tetracycline repressor (TetR) (SEQ ID NO:11) and tetracycline promotor (TetA) (SEQ ID NO:9) from *Tn*10.

17. (amended). The method according to claim 16 characterized in that the DNA vector is [the] plasmid pTetLux1 (SEQ ID NO:3).

18. (amended). The method according to claim 2 characterized in that

- the DNA vector is a plasmid containing [the] an insect luciferase gene (SEQ ID NO:1), tetracycline repressor (TetR) (SEQ ID NO:11) and tetracycline promoter (TetA) (SEQ ID NO:9) from *Tn*10, and that

- D-luciferin is added to the mixture of the sample and the cells in order to initiate the luminescence of the cells.

19. (amended). The method according to claim 18 characterized in that the DNA vector is [the] plasmid pTetLuc1 (SEQ ID NO:1).